UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

February 26, 2013

SUBJECT: **Fluxapyroxad (BAS 700F):** Summary of Hazard and Science Policy Council (HASPOC) Meeting of January 17, 2013: Recommendations on the need for a subchronic inhalation study.

PC Code: 138009
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0056561
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: HASPOC review.
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

FROM: Kristin Rury
Executive Secretary, HASPOC
Health Effects Division (7509P)

THROUGH: Jess Rowland, Co-Chair
Anna Lowit, Co-Chair
HASPOC
Health Effects Division (7509P)

TO: Angela Howard, Toxicologist
Scott Miller, ORE Assessor
Elissa Reaves, Branch Chief
Risk Assessment Branch 4
Health Effects Division (7509P)

MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Jess Rowland, John Kough, Jonathan Chen, Julie Van Alstine, Kristin Rury, Michael Metzger, PV Shah, Ray Kent

Presenters: Angela Howard, Scott Miller

Other Attendees: Ayaad Assaad, Kelly Lowe, Matthew Lloyd, Christopher Schlosser, Myron Ottley, Jessica Kidwell, Kelly O'Rourke, Jolene Trujillo, Whang Phang, Susan Hummel, Nancy Dodd (phone),

I. PURPOSE OF MEETING:

Risk Assessment Branch 4 (RAB4) is currently preparing a Section 3 risk assessment for several proposed uses of fluxapyroxad. Based on the current 40 CFR Part 158 Toxicology Data Requirements and the potential for repeated occupational and residential exposure to fluxapyroxad, a subchronic inhalation toxicity study is required. The HED Hazard and Science Policy Council (HASPOC) met on January 17, 2013 to discuss the need for a subchronic inhalation toxicity study to support the registered uses of fluxapyroxad.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:

Fluxapyroxad is a fungicide belonging to the carboxamide class of chemicals. The fungicidal mode of action is inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes, and mycelia growth. Fluxapyroxad is currently registered as an emulsifiable concentrate for use on cereal grains, legume vegetables, oil seed crops, peanuts, pome fruit, stone fruit, root and tuber vegetables, fruiting vegetables, and cotton. Applications may be made by occupational handlers using groundboom, airblast, aerial, chemigation, and standard slurry or mist-type seed treatment equipment. Residential handlers may apply fluxapyroxad to turf using backpack, hose-end, and manually-pressurized handgun sprayers.

In the most recent risk assessment (B. Daiss, D376616, 02/22/2012), an oral point of departure (POD) of 9 mg/kg/day was used for assessing short-term inhalation risks. This POD was based on changes in thyroid hormones and thyroid follicular hypertrophy/hyperplasia at the lowest observed adverse effect level (LOAEL) of 176 mg/kg/day, in the 28-day rat oral toxicity study. An oral POD of 7.3 mg/kg/day was used for assessing intermediate-term inhalation risk. This POD was based on thyroid follicular hypertrophy/hyperplasia at the LOAEL of 35.1 mg/kg/day, in the 90-day rat oral toxicity study. The level of concern (LOC) for occupational and residential exposure via the inhalation route (both durations) is a margin of exposure (MOE) $\leq$ 100. Occupational exposure is expected to be short- and intermediate-term, while residential exposure is expected to be short-term only.

In the case of fluxapyroxad, the intermediate-term occupational inhalation MOEs range from 2,100 to 600,000. The short-term residential inhalation MOEs range from 740 to 280,000.

III. STUDY WAIVER REQUEST

a. Inhalation Study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol

particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more protective. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. ***Physical-Chemical Properties***: Consideration of vapor pressure and the Henry's law constant are essential in assessing volatilization after sprays have settled. The vapor pressure of fluxapyroxad is 6.1×10^{-11} Torr at 25 °C. The Henry's law constant is 2.988×10^{-12} atm m^3 $mole^{-1}$. However, low vapor pressure and/or Henry's law constant does not preclude exposure to aerosolized droplets or particles/dusts.

2. ***Use Pattern and Exposure Scenarios:*** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. Airblast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may also contribute to spray drift. In the case of fluxapyroxad, mixing/loading/applying emulsifiable concentrate formulations for manually-pressurized handgun applications to turf (lawns, athletic fields, and parks), results in the highest inhalation exposure to occupational handlers and mixing/loading/applying for backpack applying to turf and lawns.

3. ***Margins of Exposure (MOEs):*** MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the level of concern (LOC) will be considered in combination with other factors discussed here. In the case of fluxapyroxad, the intermediate-term occupational inhalation MOEs range from 2,100 to 600,000. The short-term residential inhalation MOEs range from 740 to 280,000.

   While the residential handler MOE is 740, the exposure scenario and POD used to derive this value contains conservative assumptions including:
   - That 5 gallons, which is the default value used for the calculation, would be applied in a single application, in a residential setting.

- That a residential handler will use a backpack sprayer to apply the product to residential turf. [Note: fluxapyroxad is available as an emulsifiable concentrate, therefore, the application requires mixing with water and multiple trips would have to be made to use the backpack sprayer to apply the default amount (5 gallons) in one setting.]
- There is a large margin between the LOAEL and the POD (i.e. NOAEL) which indicates that the actual POD would be significantly higher than the actual NOAEL established in the study. Therefore, the actual MOE would be significantly higher than the calculated MOE.

Toxicological Effects: Fluxapyroxad has low acute toxicity via the oral (Toxicity Category III), dermal (Toxicity Category III), and inhalation (Toxicity Category IV) routes. It is a slight dermal and eye irritant, but is not a dermal sensitizer. In subchronic and chronic oral studies *in* rats, mice, and dogs, the liver was determined to be the primary target organ for fluxapyroxad. The rat was the most sensitive species for all durations of exposure with secondary toxicity observed in the thyroid in rats only. An acute neurotoxicity study with fluxapyroxad showed decreased rearing and decreased motor activity. There was no evidence of neurotoxicity in response to repeated administration of fluxapyroxad. Developmental effects observed in both rats and mice (thyroid follicular hypertrophy and hyperplasia in rats and decreased defecation, food consumption, body weight/body weight gain, and increased litter loss in rabbits) occurred at the same doses as those that caused adverse effects in maternal animals, indicating no quantitative susceptibility. An immunotoxicity study in mice showed no evidence of immunotoxic effects from fluxapyroxad.

For considering a waiver request for an inhalation toxicity study, the Agency will evaluate other pesticides which share the same mode of action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive, an inhalation toxicity study may be required regardless of MOE, depending on the exposure profile. Fluxapyroxad belongs to the carboxamide class of chemicals; there are no available inhalation data for other chemicals of this class.

IV. HASPOC RECOMMENDATIONS

Based on a weight of evidence (WOE) approach, the HASPOC concludes that a subchronic inhalation toxicity study is not required for fluxapyroxad at this time. This approach considered all of the available hazard and exposure information for fluxapyroxad, including: (1) the low acute inhalation toxicity (Toxicity Category IV); (2) the physical/chemical properties of fluxapyroxad, including its low volatility (6.1×10^{-11} Torr at 25 °C) ;(3)the toxicological profile of fluxapyroxad which shows the thyroid/liver to be the target organs; and (4) the use of the oral POD results in MOEs > 1000 for all occupational exposure scenarios (2,100 to 6000,000) and for all but one residential exposure scenarios (740). The short-term MOE of 740 for this one scenario (backpack sprayer) is the result of using conservative exposure assessments. There is a large margin between the LOAEL and the POD (i.e. NOAEL) which indicates that the actual POD would be significantly

higher than the actual NOAEL established in the study. Therefore, the actual MOE would be significantly higher than the calculated MOE.